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10/666,535	09/22/2003	Hideki Ichikawa	2923-0562	5882

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EXAMINER	
ROMEO, DAVID S	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	01/22/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 01/22/2007.

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PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/666,535	ICHIKAWA ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1–14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 10/27/2006 has been entered. Claims 1–14 are pending and being examined.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 103

Claims 1–7 and 12–14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neidhardt (WO 93/16099) in view of Ron (U. S. Patent No. 5,171,579) and Avis (1990).

Applicants argue that none of the cited references address shrinkage and cohesion problems when MP52 is lyophilized. Applicants' arguments have been fully considered but they are not persuasive. In response to applicant's argument that none of the cited references address shrinkage and cohesion problems when MP52 is lyophilized, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). *Prima facie* obviousness does not require that the prior art references suggest combining their disclosures for the same reason that applicants combined them. Ron specifically suggests using mannitol as a cryoprotectant to prevent the degradation of BMPs during the lyophilization process.

Applicants argue that the Avis reference provides a general discussion of lyophilization but has nothing to do with proteins in particular; that many substances are indicated as being possible agents to make the dried-product plug occupy essentially the same volume as that of the original solution; that mannitol is only one of the many possible substances according to Avis; that the disclosure of Avis would not have guided one skilled in the art to select mannitol for use

with MP52 from the numerous recited substances. Applicants' arguments have been fully considered but they are not persuasive. According to Avis, one skilled in the art of lyophilization typically considers "the nature and stability characteristics required during the liquid state, both freshly prepared and when reconstituted for use, [as well as] the characteristics desired in the dried plug" (Avis, page 1566), when formulating a pharmaceutical or biological product. More to the point, Avis identifies the choice of excipient as a variable affecting the characteristics of the lyophilized product, i.e., "whether the lyophilized substance will be dull and spongy or sparkling and crystalline, firm or friable, expanded or shrunken, etc." (Avis, page 1566). It is fair to say that Avis identifies the choice of excipient as a result effective variable, and the identification of mannitol as the ideal lyophilization excipient for MP52 would have been within the ordinary skill in the art.

Applicants argue that Applicants have found that products used in the prior art were not successful when used with MP52 and thus the use of specific substances is not predictable from the general disclosure in the cited prior art. Applicants' arguments have been fully considered but they are not persuasive. Patentability requires novelty and unobviousness in light of the prior art, not in light of what the inventor knew and included in his patent application. Furthermore, as discussed above, the identification of mannitol as the ideal lyophilization excipient for MP52 would have been within the ordinary skill in the art.

Applicants argue that Ron does not cure the deficiencies in Avis as Ron does not suggest that mannitol is suitable for the use in a lyophilized product of MP52 either; that Ron is not directed to the lyophilization of proteins but discloses a composition comprising an osteogenic protein and a porous particulate polymer matrix; that Ron mainly deals with the porous

particulate polymer matrix for providing in situ scaffolding for the osteogenic protein; that providing the osteogenic protein in a lyophilized form in the described composition is mentioned as one possible variant; that Ron suggests that additional optional components such as cryogenic protectors might be useful and mannitol is indicated to protect from degradation during lyophilization; that however, this disclosure is part of the general description and no examples were carried out in order to show that mannitol is in fact suitable in the connection with osteogenic proteins; that the suggestion of mannitol as a possible cryogenic protector does not show that mannitol is in fact successful and it was unpredictable from Ron whether or not the use of mannitol would be helpful in context with a lyophilized MP52 product; that Ron is directed to osteogenic products in general and particularly the BMP family; that though MP52 and BMP-2 belong to the same protein family, applicants point out that they do not exhibit identical physical behavior; that properties such as solubility cannot be transferred from one protein to another since individual amino acids on the protein surface have different hydrophobicity and can also show different solution behavior and different tendencies to aggregation; that in general, it is not possible to transfer data from one protein to another even if they are in the same family; that in order to illustrate the different physical properties of these two proteins, applicants point out Patent Application WO 93/00050 by Ron; that Example 3, especially Table 4, shows that BMP-2 has a good solubility in basic amino acids, e.g. in 500 mm lysine $x \geq 0.9$ mg/ml; that in contrast to this, MP52 according to the present invention, when used with lysine (0.25-25% with 1 mg/ml of MP52, page 2 of the description), has bad solubility after lyophilization resulting in cohesion/formation of aggregate; that Applicants respectfully contend that one skilled in the art could not have predicted that mannitol could be combined with bone morphogenetic factor

human MP52 to produce a lyophilized product which avoids the drawback of volume reduction (shrink) occurring during storage and also avoids cohesion of MP52 at the time of reconstitution; that since not all cryoprotectants can be used with all proteins, applicants contend that one skilled in the art would not reasonably expect mannitol to be useful with MP52 without testing.

Applicants' arguments have been fully considered but they are not persuasive. Obviousness does not require absolute predictability, only a reasonable expectation of success, i.e., a reasonable expectation of obtaining similar properties. Ron contains the suggestion to modify Neidhardt to produce the claimed invention, and Avis contains the evidence suggesting the modification would be successful.

Claims 7–14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neidhardt (WO 93/16099) in view of Ron (U. S. Patent No. 5,171,579) and Avis (1990) as applied to claims 7 and 12–14 above and further in view of Chang (J Pharm Sci. 1996 Dec;85(12):1325-30).

Applicants argue that Chang also shows that no general predictions can be made about the lyophilization conditions for specific proteins; that Chang, on page 1325, first column, discloses that "despite the numerous freeze-thawing studies on proteins, the choice of these solutes and development of stable formulations is still largely empirical because of the lack of a full understanding of the relative importance of the various stresses arising during freezing and of mechanisms by which additives protect proteins against these stresses"; that in other words, for every protein, optimum conditions must be determined individually and cannot be predicted from the results obtained with other proteins. Applicants' arguments have been fully

considered but they are not persuasive. Chang teaches that resistance to the routinely recognized freezing-induced stresses "can be increased if solution conditions are chosen that increase the thermodynamic stability of the native state of the protein. The requisite increase in the free energy of denaturation can be achieved with numerous different cryoprotectants, including sugars, … and amino acids." Page 1325, paragraph bridging left and right columns. Therefore, although "the choice of these solutes and development of stable formulations is still largely empirical", the solution to the appropriate choice is largely well known in the art. Furthermore, Ron gives specific guidance as to the choice of appropriate cryoprotectant for BMPs.

Applicants argue that Ron states that mannitol can be used to protect BMP proteins from degradation during lyophilization; that however, MP52, is stable without mannitol; that during storage of lyophilized MP52 no obvious degradations occur and there is no formation of chemical degradation products as compared to the storage of MP52 with mannitol; that thus, one would not combine Neidhardt with Ron to prevent degradation of MP52 since MP52 does not form chemical degradation products; that mannitol is primarily used for the prevention of cohesion as well as for achieving a low water content in the present invention; that Avis and Chang do not cure the deficiencies in Ron and Neidhardt as neither of these references suggest that general predictions can be made about the lyophilization conditions for specific proteins. Applicants' arguments have been fully considered but they are not persuasive. Applicants have not pointed to any specific evidence of record that MP52, is stable without mannitol or that during storage of lyophilized MP52 no obvious degradations occur and there is no formation of chemical degradation products as compared to the storage of MP52 with mannitol. Even if such

evidence were of record, the examiner would maintain that one of ordinary skill in the art would still be motivated to make the claimed invention because Avis identifies the choice of excipient as a result effective variable, and the identification of mannitol as the ideal lyophilization excipient for MP52 would have been within the ordinary skill in the art.

Applicants argue that the argumentation in the office action with regard to the mixing ratios used is inapplicable; that the Office Action argues on pages 4 and 5 that Avis indicates that mannitol can be used as a solution of 5-25%, i.e. 50 mg/ml to 250 mg/ml; that in view of Ron, the Office Action further assumes that 2-4 mg/ml of a BMP would be used (column 2, lines 22-28); that the starting point that 2-4 mg/ml of BMP is used for lyophilization, however, is not correct; that the concentration indicated in Ron, refers to the final product, i.e. the lyophilized product after solution (including reconstitution from a lyophilized form), before it is used in patients; that when using BMPs in patients, it is important that BMPs are dissolved in high concentrations (2-4 mg/ml) so that the volume used is not too high; that before lyophilization, the volume is not as important since the solvent is removed, only the weight ratio from protein to mannitol is important; that therefore, the indication of a concentration of 2-4 mg/ml should not be considered as the calculation before lyophilization as suggested in the office action; that patent Application WO 93/00050 by Ron indicates in Example 4 that BMP-2 together with mannitol and epsilon-carboxylic acid is directly lyophilized on the matrix; that 22 µg of BMP-2 and 8 mg of mannitol are used, i.e. a mixing ratio of 1:364; that the skilled artisan would have assumed that BMPs are used with considerably higher dosages of mannitol than is the case according to the present invention with MP52 wherein the optimum mixing ratio from 1:5-50 is sufficient. Applicants' arguments have been fully considered but they are not

persuasive. Ron teaches:

> The osteogenic proteins can be utilized in the form of a pharmaceutically acceptable solution (including reconstitution from a lyophilized form). It is optimal to solubilize the osteogenic protein at concentrations of at least about 2 mg/ml, preferably about 4 mg/ml, so that a pharmaceutically effective amount of protein can be delivered without undue volumes of carrier being necessary.

Avis suggests that it is desirable for the freeze-dried product plug to occupy essentially the same volume as that of the original solution. Specifically, Avis teaches that mannitol has been found to be most useful to increase the solids content of the original solution to between approximately 5 and 25% so that the freeze-dried product plug occupies essentially the same volume as that of the original solution (page 1566, column 2, full paragraphs 1-3). If it is desirable for the freeze-dried product plug to occupy essentially the same volume as that of the original solution and if one is to reconstitute osteogenic proteins from a lyophilized form to a concentration of 2-4 mg/ml, then one would have to lyophilize a solution ~91 - 182, i.e., 2000/22 to 4000/22, times the volume of the reconstituted product in order to obtain a mixing ratio of 1:364 prior to lyophilization. Furthermore, the percentage of mannitol in the in the reconstituted product would be ~91 - 182 times the 5 and 25% mannitol concentration of the original solution. The examiner concludes applicants' argument is not reasonable. Therefore, the examiner declines to adopt the manner in which applicants have construed Ron.

The examiner did not cite, nor does the examiner rely on, WO 93/00050.

Claims 7–10 and 12–14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neidhardt (WO 93/16099), Ron (U. S. Patent No. 5,171,579), and Avis (1990) as applied to claims 7 and 12–14 above and further in view of Chang (J Pharm Sci. 1996 Dec;85(12):1325-

30) and further in view of Hansen (U. S. Patent No. 6,586,574) and in light of the MeSH definition of "poloxamer."

Applicants argue that, as discussed above, the combination of Neidhardt, Ron, Avis and Chang, does not suggest that mannitol should be used when lyophilizing MP52 in view of the fact that during storage of lyophilized MP52 no obvious degradations occur and there is no formation of chemical degradation products; that Hansen is cited only for the disclosure of surfactants for stabilization of freeze-dried proteins and does not cure the deficiencies in Neidhardt, Ron, Avis and Chang regarding the use of mannitol with MP52 in a lyophilized composition. Applicants' arguments have been fully considered but they are not persuasive. The examiner believes that he has answered all pertinent arguments in his response to applicants' arguments in the two rejection that precede the instant rejection. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

New Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 112

Claim 10 recites the limitation "the polyoxyethylenic detergent/substance" in line 1. There is insufficient antecedent basis for this limitation in the claim. There is sufficient antecedent basis for the limitation "the polyoxyethylenic detergent".

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE HTTP://PAIR-DIRECT.USPTO.GOV. CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
JANUARY 11, 2007